REMARKS/ARGUMENTS

Claim status. Claims 1 to 7, 63, and 64 are now pending. Claims 8 to 62 have been canceled.

Support for Amendments. The amendments are supported in the application as originally filed and do not add new matter. New claims 63 and 64 are supported at pages 3 to 5; page 11, lines 24-25; page 21, lines 8-15; page 26, lines 3-13; originally filed Claim 27; and the Abstract as originally filed.

Objections to the Specification under Section 112. The Examiner objected to the specification as follows.

The Examiner objected that the Abstract was too long and included phraseology from patent claim terms, citing MPEP 608.01(b). In the interest of compact prosecution, the Applicants accommodated the Examiner's request and have amended the Abstract.

The Examiner objected that the Cross-Reference to Related Applications did not include the status of the applications. In the interest of compact prosecution, the Applicants accommodated the Examiner's request and so amended the subject paragraph.

The Examiner objected to the incorporation by reference at pages 30 to 31 and requested amendments to incorporate that subject matter, along with a declaration pursuant to *In re Hawkins*. The Applicants note that the subject matter incorporated by reference at pages 30 to 31 relates to subject matter not presently claimed in the application and so respectfully request that the Examiner reconsider this objection.

Rejection under Section 112, first paragraph. The Examiner alleged that the claim language "randomized Ang-2 binding peptide" and "neither X1 nor X2 is a native protein" lacked written description support in the specification as filed. The Examiner further stated that the specification does not teach any peptide sequence of Ang-2 binding sequences nor the location or number of residues that can be randomized.

The Examiner's rejection fails to consider the definition of "randomized" (page 21, lines 8 to 15). The Examiner appears only to consider sequences derived from natural sequences and not those sequences obtained from random peptide library screening (e.g., phage display). The Applicants respectfully note that the specification provides ample teaching on how such technologies can be used to generate peptides and how such peptides can be used to form Fc fusion molecules. The working examples (pages 91 to 131) provide numerous examples of peptides directed at targets other than Ang-2. The Examiner has cited no reason to doubt that these teachings will be applicable to peptides that bind Ang-2.

The Examiner further alleges that the specification must provide evidence of possession of a claimed genus, citing *University of California v. Eli Lilly*, 43 USPQ 2d 1398 (Fed. Cir. 1997). In the *Eli Lilly* case, the patent in suit claimed mammalian insulin proteins based on the disclosure of one species' insulin protein, thus seeking to sweep in orthologs from all mammalian species without describing such proteins. The court found that such a claim breached the written description requirement of Section 112 and cited "structure, formula, chemical name" as examples of suitable written description.

In *Enzo v. Gen-Probe*, 63 U.S.P.Q.2D (BNA) 1609 (Fed. Cir. 2002), the court discussed the holding in the *Eli Lilly* case but noted, "It is not correct, however, that all functional descriptions of genetic material fail to meet the written description requirement." The *Enzo* court then quoted with approval from the MPEP Guidelines:

> In its Guidelines, the PTO has determined that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Guidelines, 66 Fed. Reg. at 1106 (emphasis added). For example, the PTO would find compliance with § 112, P 1, for a claim to an "isolated antibody capable of binding to antigen X," notwithstanding the functional definition of the antibody, in light of "the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature." Synopsis of Application of Written Description Guidelines, at 60....

The *Enzo* court then applied these principles to the claims of the patent in suit. The claims therein concerned antibodies defined by the functional characteristic of preferential binding to *N. gonorrhoeae* over *N. meningitidis*. The court found that the written description requirement was met because the functional characteristic was coupled with a "a structure that is sufficiently known or disclosed."

The presently claimed Fc-peptide fusion molecules are analogous to the antibodies of *Enzo* rather than the orthologs of *Eli Lilly*. Claim 1 includes the structural formula, satisfying the "partial structure" mentioned in the Guidelines and cited in *Enzo*. The Fc domain, which is specified in the structural formula, makes up most of the structure of the claimed molecule; compare, for example, the Fc domain of SEQ ID NO: 2 with the peptides appearing in the working examples. In *Enzo*, the term "antibody" supplied sufficient structure that, coupled with the functional characteristic, it satisfied the written description requirement. In the present

application, the structural formula supplies sufficient structure that, coupled with the functional characteristic, it satisfies the written description requirement.

Furthermore, the present specification provides even greater written description than the specification in *Enzo.* This point becomes stronger as the structure becomes more detailed, as in Claims 3 and 4. Like Claim 1, these claims present structure with even greater specificity than attended by the mere use of the word "antibody," which the *Enzo* court found sufficient.

Claims 63 and 64 also provide clear written description. In these claims, the peptide portion of the claimed structure is defined in the form of a product by process. The patent law has long held that product-by-process claims satisfy the requirements of Section 112.

Rejection under Section 112, second paragraph. The Examiner has also asked the Applicants to provide the full name for Ang-2, which is angiopoietin-2. This abbreviated name was well understood by persons of ordinary skill in the art.

The Examiner also objected to the phrase at the end of Claim 1, "wherein neither X^1 nor X^2 is a native protein." The Applicants note that the phrase was added at the request of the Examiner for the related application that became U.S. Pat. No. 6,660,843. One of ordinary skill in the art would understand that a "native" protein is a protein having a sequence as would occur in nature. Moreover, persons of ordinary skill in the art would understand this meaning from the use of "native" in the specification at:

- page 15, lines 7-26, in which "native" human TPO is contrasted with the TPO-mimetic peptides, which do not have the sequence of the native protein;
- page 18, line 26 to page 19, line 27, in which "native Fc" is defined as having a sequence of a fragment digested from whole antibody and "Fc variant" is defined as having a sequence modified from native Fc;
- pages 64-65, describing preparation of Fc variants by modifying native Fc;
- page 77, lines 26-29, describing the use of the claimed compounds as agonists, mimetics, or antagonists of the "native" ligands of the proteins of interest (targets) of the claimed compounds; and
- page 93, lines 11 to 15, comparing the activity of TPO-mimetic peptides to the "native" TPO protein.

In view of the specification and the understanding of those of ordinary skill in the art, there is no indefiniteness introduced by the cited language in Claim 1.

Double patenting. The Examiner rejected the claims under the doctrine of obviousness-type double patenting over the '286 application. That application does not include a limitation to ang-2 binding peptides. The Applicants dispute the Examiner's allegations: The

'286 application does not recite ang-2 binding activity as a parameter of the claims therein. Thus, the claims of the applications are at best related as genus and species. Nevertheless, the Applicants wish to further prosecution of this application and so have enclosed a terminal disclaimer signed by the Applicants' attorney.

Rejection under Section 103. The Examiner contended that Claims 1-7 were invalid under Section 103 over Cerretti *et al.* (WO 00/75323) with no combining reference cited.

In particular, the examiner relied on passages in Cerretti concerning soluble Tek multimers (page 6, lines 10-15); Tek variants (page 8, line 4 to page 9, line 6); Tek antibodies, including phage display antibodies (page 14, lines 15-24); binding of Tek-Fc fusion polypeptides to angiopoietin (Example 4, page 22 *et seq.*); and degenerate Tek nucleic acid sequences (page 9, lines 35-36). The examiner also conceded that, "Cerretti does not disclose a fusion protein of Fc wherein the Ang-2 binding [molecule] is randomized." For reasons discussed below, neither these passages nor any other teaching in Cerretti *et al.* renders the claimed subject matter obvious.

The Tek antibodies bind to Tek rather than to a Tek ligand such as ang-2. Thus, Tek antibodies have a different mechanism of action from the ang-2 binding molecules of the present invention. As there are other ligands for Tek, such as ang-1 (page 2, line 35), one of ordinary skill in the art would expect this difference in mechanism to lead to different biological activity.

The degenerate nucleic acids do not teach variation from the Tek sequence at all. To the contrary, a degenerate sequence by definition maintains the encoded amino acid sequence. The passage cited by the examiner makes clear that the degenerate nucleic acids encode "the same amino acid sequence" (page 9, line 35).

As for the soluble Tek polypeptides, multimers, Fc fusion molecules, and variants, they maintain all or a substantial portion of the Tek sequence. The examiner argued that:

> ...[R]andomization would have been obvious to one having ordinary skill in the art in view of the teachings of Cerretti of variants of the Ang-2 binding peptide i.e., Tek polypeptide, wherein one to ten amino acids are varied in a random manner. Such variations in the amino acids would suggest random amino acids. One having ordinary skill in the art would be motivated to randomized [sic] portions of the Ang-2 binding molecule (i.e., Tek). Randomization produces a diverse or more variants that leads to the discovery of lead compounds with better pharmacological effect.

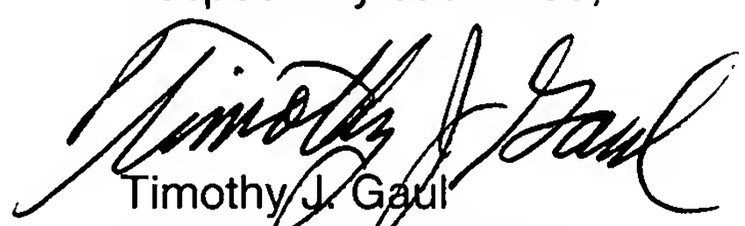
(Office Action at pages 9-10). This argument, however, appears to apply an "obvious to try" standard of obviousness, which has been explicitly rejected by the Court of Appeals for the

Federal Circuit. *In re O'Farrell,* 853 F. 2d 894 (Fed. Cir. 1988). Moreover, the randomized ang-2 binding peptides used in the claimed molecules have sequences that are not tied to the Tek sequence; as noted in the specification, they can result from such techniques as phage display technology, which starts with a library of random sequences rather than variations from a known sequence having the desired activity.

Finally, the Examiner's argument ignores that Cerretti *et al.* teach a limit of variation of 10 amino acids in the Tek polypeptide sequence. The soluble Tek polypeptide taught by Cerretti *et al.* has a sequence of hundreds of amino acids. So, in its teaching of variants, Cerretti *et al.* teach not only variation of up to 10 amino acids but also *adherence* to a sequence of hundreds of amino acids of the soluble Tek polypeptide. Thus, Cerretti *et al.* can be read as teaching away from the claimed invention, which relies on no adherence to the Tek sequence whatsoever.

Conclusion. In light of the foregoing amendments and remarks, the Applicants respectfully request reconsideration of the Office Action, entry of all amendments, and allowance of all claims.

Respectfully submitted,



Please send all future correspondence to:
U.S. Patent Operations/ TJG
Dept. 430, M/S 27-4-A
AMGEN INC.
One Amgen Center Drive
Thousand Oaks, California 91320-1799

Timothy J. Gaul
Attorney for Applicant
Registration No.: 33,111
Phone: (805) 447-2688
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